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ABSTRACT BOOK

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Background: The additional benefit of achieving major molecular response (MMR) in patients with Complete Cytogenetic Response (CCyR) response is still under debate, and therefore, patients with CCgR without MMR after 12 months of treatment are considered as a "warning" by European LeukemiaNet (ELN) recommendations. Several clinical trials have shown how patients treated with imatinib front line and classified as late warning responders can benefit from treatment changed to nilotinib in terms of improving molecular response. However, there are no data regarding to treatment change to dasatinib in this group of patients
Aims: To evaluate the efficacy and safety of treatment change to dasatinib in patients treated with imatinib first line with late suboptimal response (patients with CCyR without MMR after at least 18 months of treatment) by the ELN 09 recommendations
Methods: We are presenting preliminary results of the first 18 patients enrolled in the phase II DASAPOST study (NCT01802450). Main inclusion criteria were patients treated with late suboptimal response by the ELN09 (CCyR without MMR after 18 months of treatment). Previous treatment with imatinib 600mg (but not 800mg) was allowed. Median exposure to imatinib before dasatinib was 5.1 years (1.8-12.2). Sokal risk groups % (L/I/H) was 22.5%, 55% and 22.5%. Median age was 56 years (34-77). Primary end point was the achievement of MMR after 6 months of dasatinib. Secondary endpoints were to assess the efficacy of dasatinib in terms of depth and kinetics of molecular response, as well as the relationship of response with lymphocyte alterations. Responses evaluations were performed following indications of the ELN. All BCR-ABL/ABL (IS) measurements were centralized in an EUTOS laboratory.
Results: Clinical: Eighteen patients have been enrolled in the study. Median follow up at data cut-off was 262 days (21-380). Three out of 18 (16%) patients had discontinued dasatinib due to side effects (pancreatitis, pleural effusion and low grade, persistent side effects (fever, arthralgias, anemia and asthenia). 16/18 patients have been evaluated at 3 months, 12 at 6 months and 6 at 12 months. Cumulative incidences by ITT of MMR calculated by competing risks by 3 and 6 months were 50 and 83%. However, for patients who reached the 6 months assessment frequencies of MMR and MR4.5 were 85% and 42% respectively. No patient have lost CCyR while 1 patient in MR4.5 lost MMR. 1 patient had reduced dasatinib dose to 70mg due to congestive heart failure (patient achieved and maintained undetectable molecular response). Immunological: Lymphocyte counts were done before and after dasatinib intake at baseline, at 3 and 6 months, observing an increment of counts post intake in most patients. At baseline the median increase post intake was 1,79 fold (0,98-3,2). There was no significant association between this increment and MMR at 3M (MMR at 6 months was not studied, as most patients obtained this response at that timepoint).
Summary and Conclusions: Our study shows, for the first time to our knowledge, that in patients treated with Imatinib and late suboptimal (warning) responses, switch to Dasatinib induced MMR in 83% of the patients, although 16% discontinued treatment because of toxicity. No association was found between lymphocyte "mobilization" post intake and response. Dasatinib appears to have a good benefit/ risk ratio in this type of patients. More details on the immunologic studies will be provided.

E1118

OPTIMIZATION OF THERAPEUTIC DOSES OF RADOTINIB FOR CHRONIC MYELOID LEUKEMIA BASED ON EXPOSURE-RESPONSE RELATIONSHIP ANALYSES

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Background: BCR-ABL1 tyrosine kinase inhibitors (TKIs) have been administered as fixed doses for adult patients with chronic myeloid leukemia (CML). However, due to the wide inter-individual variability in the pharmacokinetics of TKIs and increasing evidence supporting the relationship between drug exposure and the efficacy and toxicity of these agents, there may be potential benefits of TKI dose individualization based on body size. Radotinib is a selective second generation BCR-ABL1 TKI and a phase 2 study was previously conducted in patients with TKI failed CP CML.
Aims: Using the data from the phase 2 study, radotinib exposure-efficacy and -safety relationship analyses were conducted to explore the dosing methods that will potentially improve the efficacy and safety profiles of radotinib.
Methods: The efficacy and safety data were collected for 12 months after the initiation of radotinib therapy from a multi-center phase 2 study conducted in 77 CP CML patients resistant and/or intolerant to other TKIs. All patients received radotinib 400 mg twice daily until a dose-limiting toxicity (DLT) appeared, after which the dose was reduced to 300 mg twice daily. The relationships between the body weight-adjusted dose (Dose/wt) and the probability of achieving major cytogenetic response or experiencing DLT were explored using a logistic regression method. The analyses were repeated using body-surface-area-adjusted dose (Dose/BSA). Upon a stratification of the patients based on Dose/wt or Dose/BSA, time-to-first DLT curves were compared using a Kaplan-Meier method.
Results: *Efficacy.* No significant associations were found between radotinib Dose/wt or Dose/BSA and major cytogenetic response at Months 1, 3 and 6. *Safety.* Positive correlations were observed between radotinib Dose/wt and the probabilities of first DLT occurrence at Months 3 (p=0.002), 6 (p=0.003), 9 (p=0.004), and 12 (p=0.007). Similar positive correlations were observed for Dose/BSA. Statistically significant differences were evident in the Kaplan-Meier curves of DLT between various Dose/wt groups, particularly between the groups of Dose/wt <6 mg/kg and Dose/wt ≥6 mg/kg (p=0.008) with the median time to first DLT being 259 and 83 days, respectively. At the cut-off of 6 mg/kg, the patient weighs 66.7 kg. A 2-tier weight-based dosing method was recommended to reduce the probability of DLT: radotinib 300 mg or 400 mg twice daily for patients weighing ≤65 kg or >65 kg, respectively.
Summary and Conclusions: The probability of DLT increased without improvement in efficacy as the Dose/wt or Dose/BSA of radotinib increased. Therefore, a lower initial radotinib dose of 300 mg twice daily is recommended for CP CML patients weighing ≤65 kg. A randomized clinical trial would be needed to confirm the efficacy and safety of this alternative dosing regimen.

E1119

EFFICACY AND SAFETY OF DASATINIB VS. IMATINIB IN LATIN AMERICAN SUBPOPULATION FROM THE DASISION TRIAL IN PATIENTS WITH NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA (CML) IN CHRONIC PHASE (CP)

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Background: Kantarjian *et al.* reported in the phase 3 DASISION TRIAL that 519 patients with newly diagnosed CML-CP from 108 centers in 26 countries were randomized to receive dasatinib (n=259) or imatinib (n=260). Of these, 23 % (120) were from the Latin America (LA) region (23 % Argentina, 9 % Chile, 3 % Colombia, 15 % Peru, 19 % Brazil and 30% Mexico).
Aims: The main objective was to evaluate if LA results from DASISION TRIAL can be considered similar to those obtained in the overall study.
Methods: DASISION (CA180-056; NCT00481247) is a signed IC 60 month-Open Label Multinational randomized phase 3 trial comparing dasatinib 100 mg QD versus imatinib 400 mg QD in patients with CML-CP diagnosed within 3 months who had not received previous treatment for CML. All exposure, safety, and efficacy results described here were analyzed on the 120 LA patients (all randomly assigned to receive dasatinib (n=63) or imatinib (n=57)) in comparison to the total patients treated (including Latin American patients), here referred to as "all randomized". The efficacy and safety were assessed by using data obtained during the initial 3 years period of the trial.
Statistical Methods: Comparison of the rates was performed for p=0.05 (two-tailed). Response (efficacy variables) and AEs rates were estimated with their 95% confidence intervals (CIs) when needed. The difference in rates between the 2 treatment groups was tested by using Pearson Chi square Test. PFS and OS by treatment group were estimated via the Kaplan-Meier product-limit method. Due to the fact that the 120 LA patients is a subset of the planned total enrolled population, every statistical analysis of LA was considered exploratory.
Results: Treatment was discontinued due to disease progression in 4,8 % and

7% of the cases, unacceptable toxicity in 3,2% and 8,8% of the cases in dasatinib and imatinib groups respectively. Baseline characteristics and demographics of LA patients were relatively well balanced between the two treatment groups and were similar to the overall study data with exception of baseline high Hasford risk score in LA patients that was higher in both (dasatinib and imatinib) treatment groups. At 36 months the rates of cumulative cCCyR, MMR and PFS, OS and AEs rates for patients in either arm in LA patients and in all randomized patients can be seen in Table below. AEs in LA and in all randomized patients will be described.

Table 1.

Rates (% of patients) of Efficacy Variables and Safety				
Variable	Latin America (LA)		DASISION TRIAL (All Patiens)	
	dasatinib (n=63)	imatinib (n=57)	dasatinib (n=259)	imatinib (n=260)
cCCyR within 12 months (a)	79.4	64.9	76.8	66.2 **
cCCyR within 24 months (a)	82.5	73.7	80.3	74.2
cCCyR within 36 months (a)	82.5	73.7	82.6	77.3
MMR within 12 months (b)	44.4	28.1	52.1	33.8 **
MMR within 24 months (b)	69.8	43.9 **	64.5	50.0 **
MMR within 36 months (b)	73.0	49.1 **	69.1	56.2 **
PFS within 36 months (c)	91.9	89.7	91.0	90.9
OS within 36 months (d)	91.9	92.7	93.7	93.2
DRAEs (e)	84.1	98.2	84.5	88.0
(a) confirmed Complete Cytogenetic Response; (b) Major Molecular Response; (c) Progression Free Survival; (d) Overall Survival; (e) Drug Related Adverse Events. dasatinib vs. imatinib: **: p < 0.01.				

(1) Kantarjian H, Shah N, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. New England Journal of Medicine. June 2010; 362:2260-70.
(2) Kantarjian H, Shah N, Cortes J, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). February 2012;119:1123-1129.

Summary and Conclusions: The results reported here suggest that the efficacy profiles of dasatinib vs. imatinib in LA patients are similar to those seen in the analysis of all patients worldwide. Exploratory comparisons of efficacy in LA patients of dasatinib vs. imatinib arms yielded similar trends as observed in all patients, having numerically higher rates of cumulative long-term response rate values of cCCyR and MMR in dasatinib treatment Group. Both treatment groups also experienced high rate values of PFS and OS after a 3-year follow-up. Since small sample size in LA limits the strength of conclusions for efficacy and safety, further exploration is needed to confirm any potential differences compared with the total treated population in order to increase accuracy.

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E1120

THE EFFICACY AND SAFETY OF GENERIC IMATINIB IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA (CML) AFTER SWITCHING FROM GLIVEC: UPDATED DATA FROM CERRAHPAŞA CML COHORT

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Background: Imatinib is the standart of care in patients with chronic myeloid leukemia (CML). Generic imatinib (GI) has been approved in the treatment of CML in many countries including Turkey. We previously published our experience regarding the efficacy and safety of GI in patients with CML who started tyrosine kinase inhibitor (TKI) treatment with original imatinib (OI) [Glivec] but then had to switch to GI due to reimbursement policy [Eskazan AE, *et al.* Leuk Lymphoma. 2014;55:2935-7]. Among our patient cohort, the efficacy and safety of GI were comparable to those of OI. However the median duration of GI exposure in that study was 12 months, shorter than the OI treatment duration prior to switching.
Aims: The aim of this study was to update the efficacy and safety data of GI among our chronic phase CML (CML-CP) patient cohort when used sequentially after OI treatment with an extended follow-up.
Methods: Our study cohort consisted of one hundred and forty-five patients with CML-CP who were followed under OI with a median of 55 months (Figure 1). Patients on OI first switched to GI due to reimbursement policy after August 2012, and 80 patients switched to GI whereas sixty preferred to receive OI and pay the price difference from their own pockets. After a median follow-up of 12 months, the data was first analyzed in October 2013, and the generics were found to be at least non-inferior to the OI regarding efficacy and tolerability when used subsequently [Eskazan AE, *et al.* Leuk Lymphoma. 2014;55:2935-7]. We updated the data of this study after an additional follow-up of 16 months in February 2015.
Results: Since the first analysis, 74 patients received GI with a median duration of 15.5 months, and there were four patients who switched to 2nd generation TKIs (2GTKIs) due to resistance and 4 patients were lost to follow-up. The median of GI exposure in these patients after the first switch was 27 months (range, 6-32 months). In the OI group, 60 patients received Glivec with a median of 61 months and 13 months after the first switch and the first analysis, respectively. There were 3 patients who switched to 2GTKIs (2 due to resistance, one due to grade IV hepatitis), one patient was lost to follow-up, and one patient quit OI due to a planned pregnancy. Twenty-seven patients receiving OI switched to GI during the follow-up after a median of 10 months, and at the time of the analysis, the study cohort consisted of 121 patients of which 28 were still on OI whereas ninety-three were receiving GI. All of these 121 patients had durable major molecular respose (MMR), and none of the 27 patients who switched from OI to GI lost their responses during the follow-up. There were no imatinib dose reductions due to toxicities in both arms, and 4 patients had non-hematological adverse events (AEs) (myalgia in 3 and gastrointestinal in one) in the GI group whereas in the OI group there were 3 patients (myalgia in 2 and one patient had both myalgia and hepatitis) with non-hematological AEs. Among the twenty-seven patients who switched from OI to GI, two had grade I myalgia after the switch.

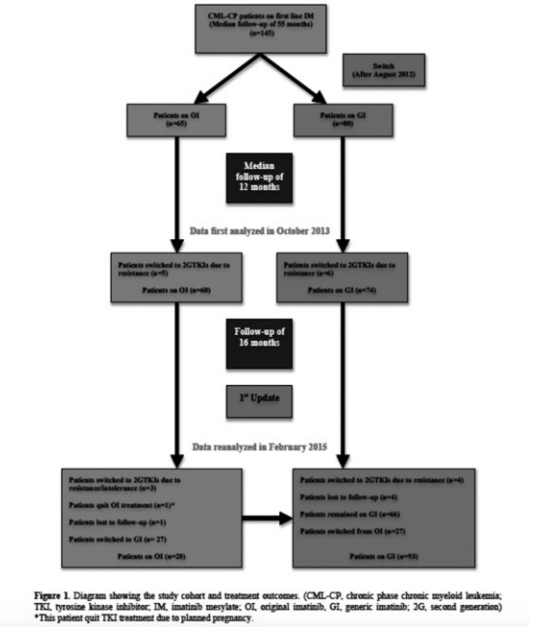

Figure 1. Diagram showing the study cohort and treatment outcomes. (CML-CP, chronic phase chronic myeloid leukemia; TKI, tyrosine kinase inhibitor; IM, imatinib mesylate; OI, original imatinib; GI, generic imatinib; 2G, second generation) *This patient quit TKI treatment due to planned pregnancy.

Figure 1.

Summary and Conclusions: With an extended follow-up, generics were still found to be comparable to Glivec regarding both efficacy and safety when used subsequently.

E1121

GENERIC IMATINIB IN NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA (CML) PATIENTS IN CHRONIC PHASE: UPDATED DATA FROM A TURKISH CML COHORT

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Background: Generic imatinib (GI) has been approved in the treatment of patients with chronic myeloid leukemia (CML)in many countries including Turkey. Since there were limited data and some concerns about the efficacy of